CELL COMMUNICATION NETWORK FACTOR 4 (CCN4/WISP1) SHIFTS MELANOMA CELLS FROM A FRAGILE PROLIFERATIVE TO A RESILIENT METASTATIC STATE AND SUPPRESSES IMMUNE SURVEILLANCE

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Key Words: Immune-oncology, Wnt signaling pathway, metastasis, secreted protein

While deregulated intracellular signaling initiates melanoma, patient survival is limited by progression and metastasis - processes often coordinated by secreted signals. Secreted signals can reinforce cell fate decisions by acting on the same cell and sustain pathology by influencing the stromal and immune cells present within the tumor microenvironment. Understanding how these secreted signals contribute to pathology remains a challenge as the relevance of a secreted signal depends highly on context. Identified by an unbiased phenotypic screen for inhibitors of immune cell crosstalk, Cell Communication Network Factor 4 (CCN4/WISP1) is a secreted matricellular protein that is upregulated in melanoma and breast cancer and correlates with a worse overall outcome. Here, I will discuss our recent in vitro and in vivo results to clarify the functional role that CCN4 plays in melanoma. Interestingly, we found that CCN4 shifts melanoma cells from a fragile proliferative to a resilient metastatic state. CCN4 drives this phenotypic shift by activating AKT Ser/Thr kinase and MEK/ERK signaling pathways that induce snail family transcriptional repressor 1 (SNAI1) expression. SNAI1 then initiates a transcriptional response similar to the epithelial-mesenchymal transition (EMT), including E-cadherin repression and fibronectin and N-cadherin induction. In vivo, knocking out CCN4 represses tumor metastasis of B16F10 and YUMM1.7 melanoma cells in syngeneic C57BL/6Ncrl and immunocompromised NOD-scid IL2Rgamma^{null} (NSG) mice. While CCN4-KO variants of B16F10 and YUMM1.7 cells grow faster that WT cells both in vitro and in NSG mice, tumors initiated by CCN4-KO variants consistently grow slower in immunocompetent hosts. This reduction in tumor growth by CCN4-KO variants also corresponds to an increase in tumor-infiltrating lymphocytes. CCN4-KO variants of B16F0 and YUMM1.7 melanoma cells are also more responsive to immune checkpoint blockade. While some mechanistic details of this heterocellular crosstalk remain unclear, the results suggest an intriguing collateral target to both enhance the efficacy of immune checkpoint blockage and inhibit metastasis.